CLAIMS

We Claim:

1. A drug delivery system for controlled protein release into a biological environment comprising:

a) a sparingly soluble biocompatible particle;

b) an effective amount of a protein or peptide deposited onto the particle forming a substantially insoluble protein-particle combination; and

c) a biocompatible polymeric matrix having dispersed therein the protein-particle combination.

2. The drug delivery system of claim 1 wherein the protein-particle combination has a biocompatible particle to protein or peptide ratio from about 1:10 to 100,000:1 by weight.

3. The drug delivery system of claim 1 wherein the protein-particle combination has a biocompatible particle to protein or peptide ratio from about 1:10 to 1000:1 by weight.

4. The drug delivery system of claim 1 wherein the protein-particle combination is present in relation to polymeric matrix at from about 0.01 to 30% by weight.

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5. The drug delivery system of claim 1 wherein said biocompatible particle is a sparingly soluble salt or oxide selected from the group consisting of zinc salts, zinc oxides, magnesium salts, magnesium oxides, calcium salts, and calcium oxides.

6. The drug delivery system of claim 1 wherein said biocompatible particle is selected from the group consisting of zinc carbonate, zinc oxide, zinc tartrate, zinc hydroxide, zinc phosphate, zinc citrate, magnesium oxide, magnesium hydroxide, magnesium carbonate, calcium oxide, calcium phosphate, calcium sulfate, calcium carbonate, and combinations thereof.

7. The drug delivery system of claim 1 wherein said protein or peptide is selected from the group consisting of oxytocin, vasopressin, adrenocorticotropic hormone, epidermal growth factor, platelet-derived growth factor (PDGF), prolactin, luteinizing hormone releasing hormone (LHRH), LHRH agonists, LHRH agonists, growth hormone, growth hormone releasing factor, insulin, erythropoietin, somatostatin, glucagon, interleukin (including IL-2, IL-11, IL-12, etc.), interferon-α, interferon-β,

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interferon-γ, gastrin, tetragastrin, pentagastrin, urogastrone, secretin, calcitonin, enkephalins, endorphins, angiotensins, thyrotropin releasing hormone (TRH), tumor necrosis factor (TNF), parathyroid hormone (PTH), nerve growth factor (NGF), granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage-colony stimulating factor (GM-CSF), macrophage-colony stimulating factor (M-CSF), heparinase, vascular endothelial growth factor (VEG-F), bone morphogenic protein (BMP), hANP, glucagon-like peptide (GLP-1), renin, bradykinin, bacitracins, polymyxins, colistins, tyrocidine, gramicidins, cyclosporins, enzymes, cytokines, antibodies, vaccines, antibiotics, antibodies, glycoproteins, and combinations thereof.

8. The drug delivery system of claim 1 wherein said protein is selected from the group consisting of human growth hormone and insulin.

9. The drug delivery system of claim 1 wherein said biocompatible polymeric matrix is selected from the group consisting of polymeric particles, implants, microcapsules, microspheres, nanospheres, polymeric gels, environment responsive polymers or gels, and combinations thereof.

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10. The drug delivery system of claim 1 wherein said biocompatible polymeric matrix is comprised of a polymer or gel material selected from the group consisting of nondegradable polymers, biodegradable polymers, absorbable polymers, bioerodible polymers, block copolymers, and combinations thereof.

11. The drug delivery system of claim 10 wherein said biocompatible polymeric matrix is comprised of a biodegradable polymer selected from the group consisting of poly(lactide)s, poly(glycolide)s, poly(lactide-co-glycolide)s, poly(lactic acid)s, poly(glycolic acid)s, poly(lactic acid-co-glycolic acid)s, polyanhydrides, poly(ortho ester)s, poly(ε-caprolactone), poly(hydroxybutyric acid), polyaminoacids, and blends and copolymers thereof.

12. The drug delivery system of claim 10 wherein said biocompatible polymeric matrix is a block copolymer selected from the group consisting of A-B-A block copolymers, B-A-B block copolymers, A-B block copolymers, and combinations thereof, and wherein said A block is a biodegradable polymer selected from

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the group consisting of poly(lactide)s, poly(glycolide)s, poly(lactide-co-glycolide)s, poly(lactic acid)s, poly(glycolic acid)s, poly(lactic acid-co-glycolic acid)s, polyanhydrides, poly(ε-caprolactone)s, poly(hydroxybutyric acid)s, poly(aminoacids)s, poly(ortho ester)s, and blends and copolymers thereof, and said B block is polyethylene glycol.

13. The drug delivery system of claim 10 wherein said biocompatible polymeric matrix is comprised of a nondegradable polymer selected from the group consisting of polyacrylates, polyacrylate esters, silicone rubbers, poloxamers, tetronics, polyethylenes, poly(methyl methacrylate)s, polymethyl methacrylate esters, polystyrenes, ethylene-vinyl acetate copolymers, polyethylene-maleic anhydride copolymers, polyamides, polymers of ethylene-vinyl acetates, acyl substituted cellulose acetates, nondegradable polyurethanes, poly(vinyl chloride)s, poly(vinyl fluoride)s, poly(vinyl imidazole)s, chlorosulphonate polyolefins, poly(ethylene oxide)s, and blends and copolymers thereof.

14. The drug delivery system of claim 1 wherein the protein or peptide is deposited onto a surface of the particle.

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15. The drug delivery system of claim 1 wherein a plurality of protein or peptide molecules are present, a first portion of said plurality of protein or peptide molecules are deposited on the particle and dispersed within the polymeric matrix, and a second portion of said plurality of protein or peptide molecules are dispersed within the polymeric matrix.

16. The drug delivery system of claim 1 further comprising a second protein or peptide.

17. The drug delivery system of claim 16 wherein the second protein or peptide is deposited on the particle dispersed within the polymeric matrix.

18. The drug delivery system of claim 16 wherein the second protein or peptide is dispersed within the polymeric matrix.

19. The drug delivery system of claim 16 wherein a plurality of second protein or peptide molecules are present, a first portion of said plurality of second protein or peptide molecules are deposited on the particle and dispersed within the

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polymeric matrix, and a second portion of said plurality of second protein or peptide molecules are dispersed within the polymeric matrix.

20. A method for controlled delivery of a protein to a warm-blooded animal comprising:

a) depositing a protein or peptides onto a sparingly soluble biocompatible particle to form a protein-particle combination;

b) loading the protein-particle combination in a biocompatible polymeric matrix; and

c) administering the loaded biocompatible polymeric matrix to a warm-blooded animal.

21. The method of claim 20 wherein the protein-particle combination has a biocompatible particle to protein or peptide ratio from about 1:10 to 100,000:1 by weight.

22. The method of claim 20 wherein the protein-particle combination has a biocompatible particle to protein or peptide ratio from about 1:10 to 1000:1 by weight.

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23. The method of claim 20 wherein the protein-particle combination is present in relation to polymeric matrix at from about 0.01 to 30% by weight.

24. The method of claim 20 wherein the loaded biocompatible polymeric matrix is delivered by a route selected from the group consisting of parenteral, ocular, topical, implantation, inhalation, vaginal, buccal, transmucosal, transurethral, rectal, nasal, pulmonary, and combinations thereof.

25. The method of claim 24 wherein the route of administration is parenteral.

26. The method of claim 20 wherein said biocompatible particle is a sparingly soluble salt or oxide selected from the group consisting of zinc salts, zinc oxides, magnesium salts, magnesium oxides, calcium salts, and calcium oxides.

27. The method of claim 20 wherein said sparingly soluble particle is selected from the group consisting of zinc carbonate, zinc oxide, zinc tartrate, zinc hydroxide, zinc

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phosphate, zinc citrate, magnesium oxide, magnesium hydroxide, magnesium carbonate, calcium oxide, calcium phosphate, calcium sulfate, calcium carbonate, and combinations thereof.

28. The method of claim 20 wherein said protein or peptide is selected from the group consisting of oxytocin, vasopressin, adrenocorticotropic hormone, epidermal growth factor, platelet-derived growth factor (PDGF), prolactin, luteinizing hormone releasing hormone (LHRH), LHRH agonists, LHRH agonists, growth hormone, growth hormone releasing factor, insulin, erythropoietin, somatostatin, glucagon, interleukin (including IL-2, IL-11, IL-12, etc.), interferon-α, interferon-β, interferon-γ, gastrin, tetragastrin, pentagastrin, urogastrone, secretin, calcitonin, enkephalins, endorphins, angiotensins, thyrotropin releasing hormone (TRH), tumor necrosis factor (TNF), parathyroid hormone (PTH), nerve growth factor (NGF), granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage-colony stimulating factor (GM-CSF), macrophage-colony stimulating factor (M-CSF), heparinase, vascular endothelial growth factor (VEG-F), bone morphogenic protein (BMP), hANP, glucagon-like peptide (GLP-1), renin, bradykinin, bacitracins, polymyxins, colistins, tyrocidine, gramicidins, cyclosporins,

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enzymes, cytokines, antibodies, vaccines, antibiotics, antibodies, glycoproteins, and combinations thereof.

29. The method of claim 20 wherein said protein is selected from the group consisting of human growth hormone and insulin.

30. The method of claim 20 wherein said biocompatible polymeric matrix is selected from the group consisting of polymeric particles, implants, microcapsules, microspheres, nanospheres, polymeric gels, environment responsive polymers or gels, and combinations thereof.

31. The method of claim 20 wherein said biocompatible polymeric matrix is comprised of a polymer material selected from the group consisting of nondegradable polymers, biodegradable polymers, absorbable polymers, bioerodible polymers, block copolymers, and combinations thereof.

32. The method of claim 31 wherein said biocompatible polymeric matrix is comprised of a biodegradable polymer selected from the group consisting of poly(lactide)s,

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poly(glycolide)s, poly(lactide-co-glycolide)s, poly(lactic acid)s, poly(glycolic acid)s, poly(lactic acid-co-glycolic acid)s, polyanhydrides, poly(ortho ester)s, poly(ε-caprolactone), poly(hydroxybutyric acid), polyaminoacids, and blends and copolymers thereof.

33. The method of claim 31 wherein said biocompatible polymeric matrix is a block copolymer selected from the group consisting of A-B-A block copolymers, B-A-B block copolymers, A-B block copolymers, and combinations thereof, and wherein said A block is a biodegradable polymer selected from the group consisting of poly(lactide)s, poly(glycolide)s, poly(lactide-co-glycolide)s, poly(lactic acid)s, poly(glycolic acid)s, poly(lactic acid-co-glycolic acid)s, polyanhydrides, polycaprolactones, poly(ε-caprolactone)s, poly(hydroxybutyric acid)s, poly(aminoacids)s, poly(ortho ester)s, and blends and copolymers thereof, and said B block is polyethylene glycol.

34. The method of claim 31 wherein said biocompatible polymeric matrix is comprised of a nondegradable polymer selected from the group consisting of polyacrylates, polyacrylate esters, silicone rubbers, poloxamers, tetronics,

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polyethylenes, poly(methyl methacrylate)s, polymethyl methacrylate esters, polystyrenes, ethylene-vinyl acetate copolymers, polyethylene-maleic anhydride copolymers, polyamides, polymers of ethylene-vinyl acetates, acyl substituted cellulose acetates, nondegradable polyurethanes, poly(vinyl chloride)s, poly(vinyl fluoride)s, poly(vinyl imidazole)s, chlorosulphonate polyolefins, poly(ethylene oxide)s, and blends and copolymers thereof.

35. The method of claim 20 wherein a plurality of protein or peptide molecules are present, a first portion of said plurality of protein or peptide molecules are deposited on the particle and dispersed within the polymeric matrix, and a second portion of said plurality of protein or peptide molecules are dispersed within the polymeric matrix.

36. The method of claim 20 further comprising a second protein or peptide.

37. The method of claim 36 wherein the second protein or peptide is deposited on the particle dispersed within the polymeric matrix.

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38. The method of claim 36 wherein the second protein or peptide is dispersed within the polymeric matrix.

39. The method of claim 36 wherein a plurality of second protein or peptide molecules are present, a first portion of said plurality of second protein or peptide molecules are deposited on the particle and dispersed within the polymeric matrix, and a second portion of said plurality of second protein or peptide molecules are dispersed within the polymeric matrix.

40. A method of preparing a protein delivery system comprising:

a) depositing a protein or peptide onto a sparingly soluble biocompatible particle to form a protein-particle combination; and

b) loading the protein-particle combination in a biocompatible polymeric matrix.

41. The method of claim 40 wherein the protein-particle combination has a biocompatible particle to protein or peptide ratio from about 1:10 to 100,000:1 by weight.

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17 42. The method of claim 40 wherein the protein-particle combination has a biocompatible particle to protein or peptide ratio from about 1:10 to 1000:1 by weight.

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18 43. The method of claim 40 wherein the protein-particle combination is present in relation to polymeric matrix at from about 0.01 to 30% by weight.

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19 44. The method of claim 40 wherein the protein or peptide is deposited onto the particle by a mechanism selected from the group consisting of adsorption, absorption, and coprecipitation.

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20 45. The method of claim 40 wherein the protein or peptide is deposited onto a surface of the particle.

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21 46. The method of claim 40 wherein said biocompatible particle is a sparingly soluble salt or oxide selected from the group consisting of zinc salts, zinc oxides, magnesium salts, magnesium oxides, calcium salts, and calcium oxides.

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47. The method of claim 40 wherein said sparingly soluble particle is selected from the group consisting of zinc carbonate, zinc oxide, zinc tartrate, zinc hydroxide, zinc phosphate, zinc citrate, magnesium oxide, magnesium hydroxide, magnesium carbonate, calcium oxide, calcium phosphate, calcium sulfate, calcium carbonate, and combinations thereof.

48. The method of claim 30 wherein said protein or peptide is selected from the group consisting of oxytocin, vasopressin, adrenocorticotropic hormone, epidermal growth factor, platelet-derived growth factor (PDGF), prolactin, luteinizing hormone releasing hormone (LHRH), LHRH agonists, LHRH agonists, growth hormone, growth hormone releasing factor, insulin, erythropoietin, somatostatin, glucagon, interleukin (including IL-2, IL-11, IL-12, etc.), interferon-α, interferon-β, interferon-γ, gastrin, tetragastrin, pentagastrin, urogastrone, secretin, calcitonin, enkephalins, endorphins, angiotensins, thyrotropin releasing hormone (TRH), tumor necrosis factor (TNF), parathyroid hormone (PTH), nerve growth factor (NGF), granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage-colony stimulating factor (GM-CSF), macrophage-colony stimulating factor (M-CSF), heparinase, vascular endothelial

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growth factor (VEG-F), bone morphogenic protein (BMP), hANP, glucagon-like peptide (GLP-1), renin, bradykinin, bacitracins, polymyxins, colistins, tyrocidine, gramicidins, cyclosporins, enzymes, cytokines, antibodies, vaccines, antibiotics, antibodies, glycoproteins, and combinations thereof.

24 49. The method of claim 40 wherein said protein is selected from the group consisting of human growth hormone and insulin.

25 50. The method of claim 40 wherein said biocompatible polymeric matrix is selected from the group consisting of polymeric particles, implants, microcapsules, microspheres, nanospheres, polymeric gels, environment responsive polymers or gels, and combinations thereof.

26 51. The method of claim 40 wherein said biocompatible polymeric matrix is comprised of a polymer material selected from the group consisting of nondegradable polymers, biodegradable polymers, absorbable polymers, bioerodible polymers, block copolymers, and combinations thereof.

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27 52. The method of claim 26 wherein said biocompatible polymeric matrix is comprised of a biodegradable polymer selected from the group consisting of poly(lactide)s, poly(glycolide)s, poly(lactide-co-glycolide)s, poly(lactic acid)s, poly(glycolic acid)s, poly(lactic acid-co-glycolic acid)s, polyanhydrides, poly(ortho ester)s, poly(ε-caprolactone), poly(hydroxybutyric acid), polyaminoacids, and blends and copolymers thereof.

28 53. The method of claim 26 wherein said biocompatible polymeric matrix is a block copolymer selected from the group consisting of A-B-A block copolymers, B-A-B block copolymers, A-B block copolymers, and combinations thereof, and wherein said A block is a biodegradable polymer selected from the group consisting of poly(lactide)s, poly(glycolide)s, poly(lactide-co-glycolide)s, poly(lactic acid)s, poly(glycolic acid)s, poly(lactic acid-co-glycolic acid)s, polyanhydrides, poly(ε-caprolactone)s, poly(hydroxybutyric acid)s, poly(aminoacids)s, poly(ortho ester)s, and blends and copolymers thereof, and said B block is polyethylene glycol.

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29 54. The method of claim 51 wherein said biocompatible polymeric matrix is comprised of a nondegradable polymer selected from the group consisting of polyacrylates, polyacrylate esters, silicone rubbers, poloxamers, tetronics, polyethylenes, poly(methyl methacrylate)s, polymethyl methacrylate esters, polystyrenes, ethylene-vinyl acetate copolymers, polyethylene-maleic anhydride copolymers, polyamides, polymers of ethylene-vinyl acetates, acyl substituted cellulose acetates, nondegradable polyurethanes, poly(vinyl chloride)s, poly(vinyl fluoride)s, poly(vinyl imidazole)s, chlorosulphonate polyolefins, poly(ethylene oxide)s, and blends and copolymers thereof.

30 55. A drug delivery system for controlled protein release into a biological environment comprising:

a) a sparingly soluble biocompatible particle selected from the group consisting of zinc salts, zinc oxides, magnesium salts, magnesium oxides, calcium salts, calcium oxides, and combinations thereof;

b) an effective amount of a protein or peptide deposited onto the particle forming a substantially insoluble protein-particle combination, wherein the protein-particle combination

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has a biocompatible particle to protein or peptide ratio from about 1:10 to 100,000:1 by weight; and

c) a biocompatible polymeric matrix having dispersed therein the protein-particle combination, wherein the protein-particle combination is present in relation to polymeric matrix at from about 0.01 to 30% by weight.

31 56. A drug delivery system for controlled protein release into a biological environment comprising:

a) a sparingly soluble biocompatible particle;

b) an effective amount of a protein or peptide deposited onto the particle forming a substantially insoluble protein-particle combination; and

c) a biocompatible polymeric matrix said comprised of a polymer or gel material selected from the group consisting of nondegradable polymers, biodegradable polymers, absorbable polymers, bioerodible polymers, block copolymers, and combinations thereof, said polymeric matrix in a form selected from the group consisting of polymeric particles, implants, microcapsules, microspheres, nanospheres, polymeric gels, environment responsive polymers or gels, and combinations

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thereof, said polymeric matrix having dispersed therein the protein-particle combination.

AMENDMENT (marked-up version)

Please cancel claim 48.

Please add new claim 57 as follows: 15

23 ~~57~~. (New) The method of claim ~~40~~ wherein said protein or peptide is selected from the group consisting of oxytocin, vasopressin, adrenocorticotropic hormone, epidermal growth factor, platelet-derived growth factor (PDGF), prolactin, luteinizing hormone releasing hormone (LHRH), LHRH agonists, LHRH agonists, growth hormone, growth hormone releasing factor, insulin, erythropoietin, somatostatin, glucagon, interleukin (including IL-2, IL-11, IL-12, etc.), interferon-α, interferon-β, interferon-γ, gastrin, tetragastrin, pentagastrin, urogastrone, secretin, calcitonin, enkephalins, endorphins, angiotensins, thyrotropin releasing hormone (TRH), tumor necrosis factor (TNF), parathyroid hormone (PTH), nerve growth factor (NGF), granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage-colony stimulating factor (GM-CSF), macrophage-colony stimulating factor (M-CSF), heparinase, vascular endothelial growth factor (VEG-F), bone morphogenic protein (BMP), hANP, glucagon-like peptide (GLP-1), renin, bradykinin, bacitracins, polymyxins, colistins, tyrocidine, gramicidins, cyclosporins, enzymes, cytokines, antibodies, vaccines, antibiotics, antibodies, glycoproteins, and combinations thereof.

No new matter has been added by virtue of these amendments.